PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	27 JAN 2005
Applicant's or agent's file reference 10589-34-228	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/09590	26 March 2004 (26.03.2004)	27 March 2003 (27.03.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A01N 61/00; C12Q 1/00; G01N 33/566, 33/573, 33/574. and US Cl.: 435/ 4, 6, 7.2, 7.21, 41, 69.2, 91.3, 183 ; 514/ 1, 2

Applicant

PTC THERAPEUTICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 25

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 25

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest
   - ☐ not paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-24

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2-6,9,10,12,14,16 and 22-24	YES
	Claims	1,7,8,11,13,15 and 17-21	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-24	NO
Industrial applicability (IA)	Claims	1-24	YES
	Claims	NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 18-19 lack novelty under PCT Article 33(2) as being anticipated by US Pat. No. 5,726,195A (HILL et al.)

Hill et al. disclose small molecule antifungal (e.g anti-yeast) compounds for treating microbial infections when administered to a host (e.g. human). These compounds inhibit tRNA enzymes (e.g. synthetases) and comprise structure within the scope of the presently claimed invention (e.g. see examples and patent claims). The ability to inhibit tRNA ligase is inherently present. In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 20-21 lack novelty under PCT Article 33(2) as being anticipated by US Pat. No. 6,446,032 B1 (SCHIMMEL)

Schimmel discloses small molecule (e.g. see bottom of col. 27-28) antiproliferative (e.g chemotherapeutic agents: see col. 3) compounds for treating cancer when administered to a host (e.g. human). These RNA (e.g. tRNA) binding compounds comprise structure within the scope of the presently claimed invention (e.g. see col. 27-28, examples and patent claims). The ability to inhibit tRNA ligase is inherently present due to the ability of these compounds to bind tRNA. In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 18-21 lack novelty under PCT Article 33(2) as being anticipated by WO 01/25486 (RANA).

The Rana reference discloses assay-derived tRNA inhibiting (e.g.binding: see e.g. bottom of page 9-top of top of page 10; and claims, especially claims 1,2, 28-30, 40-43,) compounds within the scope of the presently claimed invention (e.g. claims 25-26) which are antiproliferative and antifungal for use in treating fungal (e.g. yeast: see i.e. claims 47-48) infections (e.g. see page 10-11 et al.) and antiproliferative disorders (e.g. cancer; i.e. see claim 46) when administered to humans. The ability to inhibit tRNA ligase is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 18-21 lack novelty under PCT Article 33(2) as being anticipated by WO 02/083837A1(ALMSTEAD).

The Almstead reference discloses assay-derived tRNA binding compounds (e.g. see pages 3-4; bottom of page 10-11) within the scope of the presently claimed invention (e.g. see pages 21-23; claim 5) which are antiproliferative and antifungal for use in treating fungal (e.g. yeast) infections and antiproliferative disorders (e.g. cancer) when administered to humans. See claims; page 12; page 39 et. al. The ability to inhibit tRNA ligase is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

Claims 18-21 lack novelty under PCT Article 33(2) as being anticipated by WO 02/083953 A1 (RANDO et al.).

The Rando et al. reference discloses assay-derived RNA binding (e.g. tRNA) compounds which effect RNA host cell factor complexes in vivo (e.g. RNA splicing: see page 10; bottom of page 12-page 13) which compounds are within the scope of the presently claimed invention (e.g. see claim 5) which are antiproliferative and antifungal for use in treating fungal (e.g. yeast) infections and antiproliferative disorders (e.g. cancer) when administered to humans. See e.g. pages 12-13; pages 47-53 et al. The ability to inhibit tRNA ligase is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In any event the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 1, 7, 8, 11, 13, 15 and 17 lack novelty under PCT Article 33(2) as being anticipated by GREER, Molecular and Cellular Biology Vol. 6, No. 2 (Feb. 1986) pages 635-644.

Greer teaches a competitive assay for joining tRNA halves (e.g. 5' and3' tRNA half molecules) in which ligation is measured between yeast ligase (e.g. a fungal tRNA splicing ligase derived from a yeast cell free extract) and T4 ligase (e.g. a "small organic" compound) as compared to a control. See e.g. Abstract; pages 638-641.

Claims 1-24 lack an inventive step under PCT Article 33(3) as being obvious over WO 01/25486 (RANA), WO 02/083837A1(ALMSTEAD) and/or WO 02/083953 A1 (RANDO et al.) in view of GREER, Molecular and Cellular Biology, HYDE-DERUYSCHER et al. Chem. & Biol. Vol. 7, No. 1 and LI et al., Science Vol. 280 (4/98).

The presently claimed invention is directed to identifying antifungal/antiproliferative compounds by screening (e.g. highthroughput) compounds (e.g. library derived) for their ability to inhibit the ligation of mammalian/yeast tRNA half molecules by inhibiting tRNA-ligase binding relative to a control.

Screening assays (e.g. highthroughput) of single compounds or compound libraries for their ability to disrupt RNA (e.g. tRNA) interactions (e.g. including splicing) in order to identify antifungal/antiproliferative drug candidates is taught by the RANA, ALMSTEAD AND/OR RANDO reference whose teaching discussed above is herby incorporated by reference in its entirety.

The RANA, ALMSTEAD AND/OR RANDO reference methods differ from the presently claimed invention by failing to explicitly teach the application of its methods to tRNA ligation assays which incorporate tRNA half molecules and tRNA ligase.

However, Li et al. teach that the tRNA splicing pathway is analogous in mammals and other organisms (e.g. fungi).

In this regard, Greer teaches a competitive assay for joining tRNA halves (e.g. 5' and3' tRNA half molecules) in which ligation is measured between yeast ligase (e.g. a fungal tRNA splicing ligase derived from a yeast cell free extract) and T4 ligase (e.g. a "small organic" compound) as compared to a control. See e.g. Abstract; pages 638-641. Greer's competititve endonuclease/ligase assays would be expected to be extrapolatable to mammalian systems in light of the Li et al. reference teaching.

Additionally, the HYDE-DERUYSCHER et. Reference teaches that high-throughput screening of "small molecule" compound libraries (e.g. phage) is ideal for screening "small molecule" enzyme inhibitors for a variety of different enzymes, including ligases.

Accordingly, it would have been obvious to utilize tRNA ligation assays (e.g. incorporating tRNA half molecules and ligages) in the highthroughput screening methods of RANA, ALMSTEAD AND/OR RANDO since these references specifically suggest screening small molecule libraries for compounds which disrupt tRNA interactions including splicing and in light of the secondary reference teaching that tRNA splicing pathway in mammals/fungi is known and analogous; and the known teaching of competitive tRNA endonuclease/ligase assays; with the desirability of using highthroughput screening of small molecular libraries for screening enzyme (e.g. ligase) binding compounds as drug candidates.

Claims 1-24 meet the criteria set out in PCT Article 33(4), and thus posess industrial applicability because the subject matter claimed can be made or used in industry.